# Increased Frequency of Ig Heavy-Chain HS1,2-A Enhancer *2 Allele in Dermatitis Herpetiformis, Plaque Psoriasis, and Psoriatic Arthritis

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The enhancer DNase-hypersensitive region 1,2 (HS1,2), a member of the Ig heavy-chain 3′ regulatory region (3′RR) cluster, is active in human B cells transfected with reporter genes and in mouse is activated in late maturation. HS1,2-A contains binding sites for several transcription factors. There are four known alleles, that is, *1, *2, *3, and *4, which differ in their lengths in transcription factor binding. We showed that in celiac disease the frequency of the *2 allele is increased. Both dermatitis herpetiformis (DH) and psoriasis can be associated with different frequencies with celiac disease. Thus, we further investigate the frequency of allele *2 in DH, plaque psoriatic, and psoriatic arthritis patients. HS1,2-A allele frequencies were investigated in 37 DH, 61 plaque psoriatic, 28 psoriatic arthritis patients, and 265 healthy donors, age- and sex-matched, from the same geographical area. The frequency of the *2 allele changes from 0.39 in controls to 0.63 in DH, 0.59 in plaque psoriasis and 0.75 in psoriatic arthritis (P between $10^{-4}$–$10^{-5}$). Our data evidence an increased frequency of the *2 allele of HS1,2-A in these cutaneous immune-related disorders. We suggest a related genetic predisposition in these pathogeneses.

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## INTRODUCTION

Susceptibility to immune diseases is considered a multigenic phenotype affected by a variety of genetic and environmental or stochastic factors (Shepshelovich and Shoenfeld, 2006). The abnormal immune response can be triggered by interactions between susceptibility genes and environmental factors. The most potent genetic influence on susceptibility to immune-disorders is the major histocompatibility complex. However, there also are non-major histocompatibility complex susceptibility alleles related to immune diseases. Various epistatic interactions are predicted to involve the multiple genes required for disease development (Wandstrat and Wakeland, 2001).

Accordingly, we predict that certain immunological pathways are common to multiple immune diseases, and other pathophysiological mechanisms are specific to a particular disease (Wandstrat and Wakeland, 2001). For example, the presence of a specific antibody in an individual's serum combined with disease-prone major histocompatibility complex haplotypes or other susceptibility loci exponentially increases the risk for that person to develop an immune disease in the future (Shepshelovich and Shoenfeld, 2006).

Plaque psoriasis (OMIM 177900) and psoriatic arthritis (OMIM 607507), together with dermatitis herpetiformis (DH) (OMIM 601230), are multi-factorial cutaneous diseases with familial incidence and immune dependence (Karell *et al.*, 2002; Bowcock, 2005). Celiac disease and DH are closely related diseases, which share a genetic background and a common pathogenesis characterized by gluten sensitivity and production of autoantibodies (Hervonen *et al.*, 2000; Karell *et al.*, 2002). Patients with DH, which is sometime referred to as the cutaneous phenotype of celiac disease, have asymptomatic or frank celiac disease and a skin rash with anti-transglutaminase (TGM) cutaneous IgA deposits. Celiac disease and DH patients both show anti-TGM type 2 autoantibodies. Sardy *et al.* (2002) have shown a difference in the pattern of anti-TGM antibodies. In fact, in addition to anti-TGM type 2 antibodies, DH patients develop a further

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*Abbreviations: DH, dermatitis herpetiformis; HS, DNase-hypersensitive region; HS1,2-A, DNase-hypersensitive A region 1,2; 3′RR, 3′ Ig heavy-chain regulatory region; TGM, transglutaminase*

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class of high-affinity antibodies against epidermal TGM or TGM type 3. Therefore, TGM3 is the dominant autoantigen in DH, explaining why skin symptoms rather than intestinal symptoms appear in a proportion of patients with gluten-sensitive disease (Sardy *et al.*, 2002).

Plaque psoriasis, a clinically heterogeneous disease with inherited susceptibility, is considered a T-cell-mediated inflammatory skin disease, but humoral immune processes have also been evaluated. Plaque psoriasis has been variously reported to be associated with IgA-related disorders such as celiac disease, dermatitis herpetiformis, linear IgA sub-epidermal bullous dermatosis, IgA nephropathy, or IgA necrotic renal glomerular vasculitis (Kallel Sellami *et al.*, 2006; Lapeyre *et al.*, 2006; Zadrazil *et al.*, 2006). Up to 16% of psoriatic patients show the presence of IgG and IgA anti-endomysial, anti-gliadin, and anti-TGM antibodies (Woo *et al.*, 2004). These celiac disease-associated antibodies in psoriatic patients are apparently correlated with greater disease activity. In particular, IgA anti-tissue TGM antibodies seems to represent a lesion-associated event (Borg, 1997). A good correlation between serum and synovial fluid anti-tissue TGM levels was found in all inflammatory bowel patients and in arthropathic lesions (Caspi *et al.*, 2006). Furthermore, psoriatic arthritis patients seem to have an increased number of lymphocytes in the duodenal mucosa and a highly significant increase in intraepithelial lymphocytes in comparison with plaque psoriasis patients (Lindqvist *et al.*, 2006). Taken together, these data strongly support the idea of IgA deregulation in these skin diseases and more generally, an immune-alteration.

The 3′ Ig heavy-chain regulatory region (3′RR) enhancer complex (Pettersson *et al.*, 1990; Chen and Birshtein, 1997; Mills *et al.*, 1997) is active in murine class switch recombination and B-cell plasma cells (Andersson *et al.*, 2000; Pinaud *et al.*, 2001). The 3′RR is present through many species from mouse to apes and the orthologous enhancers conserved (Harindranath *et al.*, 1998; Stavnezer and Amemiya, 2004; Sepulveda *et al.*, 2005).

In humans, the 3′RR is duplicated; a copy lies downstream of each of constant α-1 and constant α-2 genes (Chen and Birshtein, 1997; Mills *et al.*, 1997; Pinaud *et al.*, 1997). The human 3′RRs contain three enhancers: DNase-hypersensitive region 3 (HS3), HS1,2, and HS4. The central HS1,2 enhancers are polymorphic (see Figure 1; Mills *et al.*, 1997; Giambra *et al.*, 2005). A significant correlation of the *2 allele of DNase-hypersensitive A region 1,2 (HS1,2-A), downstream of α-1 gene, was shown in patients with IgA nephropathy, and celiac disease and systemic sclerosis (Aupetit *et al.*, 2000; Frezza *et al.*, 2004, 2007).

Therefore, we compared the frequencies of four alleles of the HS1,2-A enhancer in patients with DH, plaque psoriasis, and psoriatic arthritis with a healthy sample of the same geographical area. A significant correlation was observed in all three disorders, with an increase in *2 allele frequency.

## RESULTS

The data reported in Table 1 show the frequencies of the four alleles of the enhancer HS1,2-A in the group of patients with dermatitis herpetiformis, plaque psoriasis, psoriatic arthritis, and in a control group selected from the same geographical area and not related at least for three generations. The distribution of the four allele's frequencies is similar in these three pathological groups, but different with respect to the control sample. In the control and pathological samples, the observed genotypes were in agreement with Hardy–Weinberg expected values as reported in Table 1.

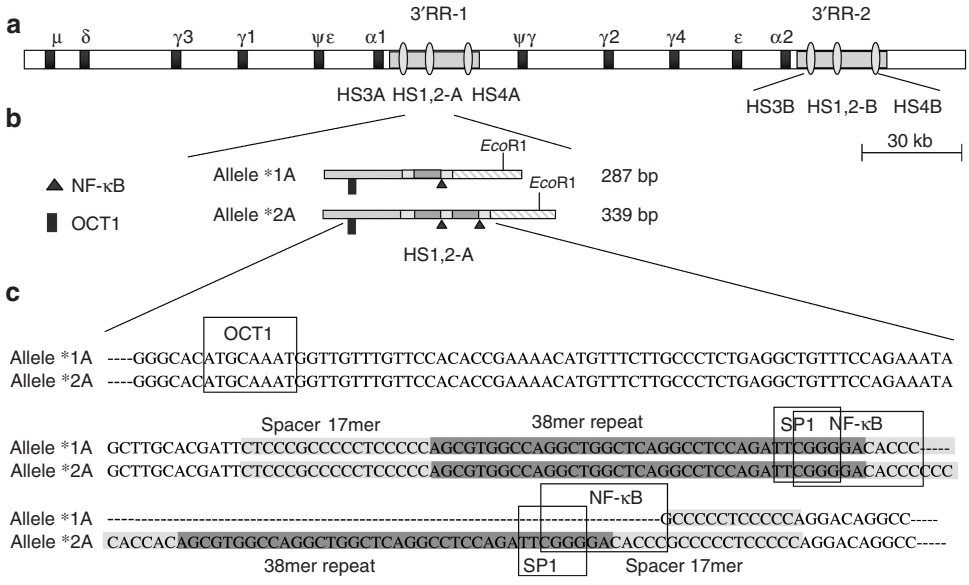


**Figure 1. The human constant genes heavy-chain locus.** (**a**) The duplication of four constant genes and relative regulatory region 3′RR-1 and 3′RR-2. (**b**) Enlarged view of the structure of HS1,2 alleles *1 and *2 with the repeated elements of 38 bp and spacers of 17 bp; the triangle shows the position of the consensus of NF-κB and SP1, and the parallelogram shows the consensus for OCT1. (**c**) Alignment of allele *1 and *2 sequences and the difference due to the duplication of the 38-mer and internal spacer. The consensus for OCT1, NF-κB, and SP1 transcription factors are highlighted by square frames.

**Table 1. Frequency ± SE of HS1,2-A alleles in patients with DH, plaque psoriasis, psoriatic arthritis, and healthy control, and Hardy–Weinberg evaluation**

| Alleles | Dermatitis herpetiformis | Plaque psoriasis | Psoriatic arthritis | Control |
|---|---|---|---|---|
| *1A | 0.297 ± 0.053 (22) | 0.344 ± 0.043 (42) | 0.214 ± 0.054 (12) | 0.449 ± 0.022 (238) |
| *2A | 0.635 ± 0.070 (47) | 0.590 ± 0.044 (72) | 0.750 ± 0.057 (42) | 0.392 ± 0.021 (208) |
| *3A | 0.014 ± 0.014 (1) | 0.008 ± 0.008 (1) | 0.018 ± 0.017 (1) | 0.059 ± 0.010 (31) |
| *4A | 0.054 ± 0.026 (4) | 0.058 ± 0.021 (7) | 0.018 ± 0.017 (1) | 0.100 ± 0.013 (53) |
| Genomes | 74 | 122 | 56 | 530 |
| Degree of freedom | 1 | 1 | 1 | 1 |
| $\chi^2$ | 4.999 | 2.088 | 0.326 | 1.685 |
| *P* | $0.05 < P < 0.025$ | $0.50 < P < 0.25$ | $0.75 < P < 0.50$ | $0.25 < P < 0.10$ |

DH, dermatitis herpetiformis; HS1,2-A, DNase-hypersensitive A region 1,2.
The number of observed genomes is indicated in parentheses.

**Table 2. Test of significance of HS1,2-A allelic frequency differences among DH, plaque psoriasis, or psoriatic arthritis patients compared with the control**

| | Dermatitis herpetiformis | Plaque psoriasis | Psoriatic arthritis |
|---|---|---|---|
| Degree of freedom | 3 | 3 | 3 |
| $\chi^2$ | 16.46 | 18.63 | 22.56 |
| *P* | 0.0008 | 0.0002 | $< 10^{-5}$ |

DH, dermatitis herpetiformis; HS1,2-A, DNase-hypersensitive A region 1,2.

**Table 3. Risk to develop DH, plaque psoriasis, or psoriatic arthritis associated with the frequency of the *2A allele**

Dermatitis herpetiformis *versus* control
Degree of freedom=1 $\chi^2$=8.291[1] *P*=0.004 OR=2.136 CI=1.29–3.53[2]

Plaque psoriasis *versus* control
Degree of freedom=1 $\chi^2$=15.025[1] *P*=0.0001 OR=2.229 CI=1.50–3.33[2]

Psoriatic arthritis *versus* control
Degree of freedom=1 $\chi^2$=17.198[1] *P*<0.0001 OR=3.681 CI=1.96–6.90[2]

CI, confidence interval; DH, dermatitis herpetiformis; OR, odds ratio.
$\chi^2$-Test and OR with CI of the different groups of patients *versus* control subjects for the *2A allele.
[1]With Yates correction.
[2]Using the approximation of Woolf.

The comparisons of the allelic frequencies between pathological and healthy groups measured by a $\chi^2$ significance test showed very low *P*-values for DH, plaque psoriasis, and psoriatic arthritis ($P < 8 \times 10^{-4}$, $P < 2 \times 10^{-4}$, and $P < 10^{-5}$, respectively), emphasizing the strong divergence from healthy group (see Table 2). In these three diseases, the frequencies of *1, *3, and *4 alleles are decreased compared with the control. Moreover, there is a dramatic increase in *2 allele frequency, which is 0.63, 0.59, 0.75 in DH, plaque psoriasis, and psoriatic arthritis, respectively, and 0.39 in the control, with an increase of 1.62, 1.50, and 1.91-fold, respectively.

These results indicate a correlation between the *2 allele's frequency increase and DH, plaque psoriasis, and psoriatic arthritis. Therefore, we measured the odds ratios with the corresponding confidence intervals, as reported in Table 3. A similar trend characterizes the three diseases and suggests that the presence of *2 allele associates to a clinical risk in developing the immune-disorders (odds ratio: 2.1, 2.2, and 3.6, respectively).

## DISCUSSION

In this report, we provide evidence that the HS1,2-A enhancer *2 allele's frequency is increased in DH, plaque psoriasis, and arthritic psoriasis. These data suggest a possible role for a particular allele of the enhancer HS1,2-A in these skin disorders. However, it should be noted that the genetic predisposition might not directly relate to cutaneous manifestations. The higher allele *2 frequency in psoriatic patients with arthritis might rather suggest a role for this allele also in the arthritic manifestations. We predict that the increased frequency of *2 allele is not a specific marker of these three pathological conditions, but a marker of a differential response of Ig induction. The *2 allele could function as a magnifier of Ig production that, in a physiological condition, could give a favorable response. In fact in the European population, this allele is present at such a high percent as 39%, impossible if there were not advantages to its presence at least in heterozygotes (Giambra *et al.*, 2006). The frequencies of *2 allele in the three pathologies compared with the control are different, with a highly significant $\chi^2$-value. The frequency is higher in DH and psoriatic arthritis than in plaque psoriasis; DH and psoriatic arthritis are in fact more rarely observed than plaque psoriasis. This difference could be attributed to the fact that a restricted number of factors are necessary and sufficient to trigger the onset of DH and psoriatic arthritis compared with those of plaque psoriasis, where many independent factors can be sufficient, and not all are necessary, to turn on the disease.

As far as the role of HS1,2-A is concerned, *in vitro* studies demonstrated an increased enhancer activity on the luciferase gene by the HS1,2-A allele *2 compared with *1 as well as for all the alleles harboring a higher number of repeats in respect to the shorter ones (Denizot *et al.*, 2001). The role of Hs1,2-A allele *2 may be then important in modifying immune or inflammatory responses in our patients. The most evident difference of allele *2 in regards to allele *1 is the presence of an extra consensus site for NF-κB and SP1 (see Figure 1). On the basis of the immunological alterations present in the disorders, the *2 allele prompts Ig production to a stronger response either in terms of activation of class switch or germinal transcription. These results may identify a role for genetic polymorphism in the immune regulation and its influence in B-cell activity. The analysis of the haplotypes of the entire 3′-regulatory region will provide more information on the role of this *cis*-acting region in immune-diseases.

In conclusion, our data add DH, plaque psoriasis, and psoriatic arthritis to the growing list of disorders associated with Ig deregulation, where the enhancer HS1,2-A may be involved. Further studies are needed to understand its role in the pathogenesis of the diseases and their progression. It is interesting to note that as of now none of the whole-genome studies in psoriasis have picked up this association. A replication of the findings by independent research groups with larger sample sizes will be necessary to confirm these data.

## MATERIALS AND METHODS

### Patients

Thirty-seven DH patients were studied (13 males, 24 females, mean age 36. 87 ± 17.68 years). Diagnosis was based on standard clinical and laboratory criteria. Granular IgA deposits in the dermal papillae of perilesional skin were evaluated. Celiac disease was associated in 28/37 (8 males, 20 females, mean age 35.50 ± 12.65 years). We have also enrolled 61 patients with plaque psoriasis (39 males, 22 females, mean age 43.91 ± 16.71 years) and 28 with psoriatic arthritis (16 females, 12 males, mean age 47.06 ± 13.70 years). Diagnosis was based on clinical criteria. To exclude association with celiac disease, all psoriatic patients were put on blood tests to assess the presence of anti-endomysial antibody (anti-EMA) antibodies. Two patients with anti-EMA antibodies were excluded.

The control group consists of 265 healthy Italian blood donors, age- and sex-matched, from the same geographical areas. Genomic DNA was extracted from total blood according to standard procedures. All participants gave written informed consent. The study was conducted according to the Declaration of Helsinki Principles and the medical ethical committees of Clinics of Roma, Messina, and Palermo approved the study.

### PCR assay

To estimate the frequencies of the four alleles of HS1,2-A (GenBank accession no.: AJ544218, AJ544219, AJ544220, AJ544221), we carried out a selective PCR, which amplified the HS1,2-A region, but not the identical inverted HS1,2-B region (Giambra *et al.*, 2005). Genomic DNA was extracted from peripheral blood nucleated cells and amplified with the primers described previously (Giambra *et al.*, 2005). The cycle conditions were changed to 94 °C at 2 minutes for the first step, followed by 94 °C at 30 seconds, 61 °C at 30 seconds, 68 °C for 5 minutes for 10 cycles, and 94 °C for 30 seconds, 59 °C for 30 seconds, 68 °C for 5 minutes for 20 cycles, and ending with 72 °C for 10 minutes. PCRs were carried out in 50 μl of reaction volume containing 2 μl of extracted DNA (50 ng), 1.5 U Platinum *Taq* DNA polymerase High Fidelity (Invitrogen, Carlsbad, CA), 15 pmoles of each primer, 1.5 mM $MgSO_4$, 50 μM each dNTP, and 1 × buffer High Fidelity (600 mM Tris-$SO_4$, pH 8.9, 180 mM [$(NH_4)_2SO_4$]; Invitrogen) by using the GeneAmp PCR System 9700 (Applied Biosystems, Foster City, CA).

To prevent carryover contamination, pre-PCR procedures were performed with dedicated equipment in a laminar flow hood, using aerosol-resistant plugged pipette tips (ART; Molecular Bio-Product, San Diego, CA). Permanent devices were sterilized by ultraviolet irradiation between usages. Negative and positive controls, without DNA template or with a control DNA of a heterozygote, were always included.

A nested second PCR to amplify the polymorphic core of the enhancer HS1,2-A was performed with 1/25 of the volume of the first PCR, avoiding carryover of the genomic DNA of the first reaction. Control reactions were performed with 4 and 10 ng of total genomic DNA and resulted in no visible amplification in those conditions on agarose gel electrophoresis. The primers for the PCRs are reported by Giambra *et al.* (2005). Cycle conditions were as follows: denaturation step, 94 °C for 5 minutes; then 94 °C for 30 seconds, 56 °C for 30 seconds, 68 °C for 60 seconds, for 30 cycles; then the last cycle at 72 °C for 2 minutes (final extension step). This second PCR was carried out with the same volumes and concentrations as in the first PCR, except for the use of 1 U of Platinum *Taq* DNA polymerase (Invitrogen). PCR products were analyzed on 2.5 % agarose gel stained with ethidium bromide.

### Statistical analysis

The frequencies of the variables considered are described in percentages. Comparisons between the frequencies of categorical variables in different groups were performed by $\chi^2$-test. *P*-value was set at 0.05. Smith's Statistical Package, version 2.80 (Pomona College, Claremont, CA), Graphpad Instat (San Diego, CA), and Stata 6.0 TM software (College Station, TX) were used for statistical analysis.

## CONFLICT OF INTEREST

The authors state no conflict of interest.

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